



ON THE CONDITIONS WHICH DETERMINE THE DISTRIBUTION OF THE COAGULATION FOLLOWING THE INTRA-VASCULAR INJECTION OF A SOLUTION OF WOOLDRIDGE'S TISSUE FIBRINOGEN.
By A. E. WRIGHT, B.A., *Trin. Coll. Camb.*, M.D. *Univ. of Dublin.*

Preliminary Communication.

THE injection of a solution of Wooldridge's tissue fibrinogens into the veins of a living dog results in thrombosis of the portal vein and its affluents, the blood in the systemic veins and arteries remaining liquid. These important facts were elicited by Wooldridge¹, and only his premature death prevented his following up this fruitful discovery.

The observations which are to be communicated here will perhaps contribute towards carrying his work a step further.

Wooldridge while describing the usual result of an injection of tissue fibrinogen to be the coagulation of the blood in the portal district alone, had not failed to observe that if the injection were made into an animal during active digestion coagula were also found in the right heart and in the pulmonary artery. The hypothesis which he put forward tentatively to explain these facts was, that the coagulation that occurred in the portal tract was due to the injected tissue fibrinogen there meeting some body which had been absorbed from the intestinal canal and which favoured coagulation. This body he supposed to be under ordinary conditions completely eliminated from the blood during its passage through the liver. In active digestion however he suggested it would be incompletely held back there, and the coagula found in the right heart would then be due to its overflow into the cardiac blood.

This hypothesis, however, becomes untenable in the light of the following facts:

¹ *Proceedings, Royal Society*, 1886.

1. The coagulation occurs in the portal district, even when the injection is made in an animal that has been kept for six or eight days without food.
2. The coagulation occurs not in the portal vascular system alone but all over the body, when the injection of tissue fibrinogen is made in an animal that has become dyspnoeic by compression of the trachea.

In evidence of this last fact the following protocol may be quoted.

Sept. 22, 1890. Fox-terrier—cannula inserted into the jugular vein, trachea compressed with a ligature; as soon as dyspnoea has become marked 25 c.c. of a solution of tissue fibrinogen were allowed to run into the jugular vein. Respiration came to an immediate stand-still. Ligature on the trachea was relaxed and the post-mortem was begun immediately. After the post-mortem had commenced the animal gave two or three of the deep “ante-mortem” gasps constantly seen in asphyxia through acute deprivation of oxygen.

P. M. *Thorax*—Jugulars and Innominate veins empty, slight clot in S.V.C., Azygos Vein clotted; right Auricle and Ventricle one solid blood clot; I.V.C. one solid clot; left Ventricle shewed a slight brightly arterialized clot; left Auricle is distended with a brightly arterialized clot forming casts of the pulmonary veins. These last were clotted right through to the lungs. On cross section the vessels in the lungs were seen to be filled with bright arterial blood clots. The Aorta is clotted solid right down to the level of the renal arteries. The aortic clot is a dark venous clot.

Heart begins to beat again when tension is relieved, and continues beating for more than a minute after all its cavities have been laid open.

Abdomen—Hepatic vein clotted, I.V.C., clotted firm down to the renal veins. Here a nick was made in the vein and the iliac veins were laid open. Blood poured out, solidifying immediately into a clot.

NOTE. The bright arterial clot in the left ventricle, left auricle and lungs was evidently blood that was oxidized in the lungs during the ‘ante-mortem’ gasps, though, of course, there is nothing to shew that it was arterial in the sense of its having freed itself from its excess of CO_2 . The dark-coloured clot in the aorta on the other hand must have passed through the lungs while the trachea was being compressed.

It having thus been established that asphyxia will bring about a condition of general coagulability of the blood, experiments were now

made with a view of determining whether an increase of the metabolism of an organ or tissue such as would probably induce a more venous condition of the blood in a particular vascular district would result in the blood in that district becoming coagulable by the injected tissue fibrinogens. The following experiments were therefore made.

1. The sciatic nerve was exposed as high as possible in the back of the right thigh. It was divided and the peripheral end was stimulated by a strong interrupted current. After the stimulation had been continued for a couple of minutes, the usual quantity 20 to 30 c.c. of Wooldridge's coagulating fluid was allowed to flow into the jugular vein, the stimulation being continued while the injection was proceeding. The animal succumbed some few seconds after the injection was completed. The post-mortem which was undertaken immediately disclosed in addition to the usual thrombosis of the portal tract a complete thrombosis of the femoral and iliac veins on the right side. The distribution of the clotting downwards accurately followed that of the branches of the sciatic nerve, the blood in the tributaries from the anterior part of the thigh remaining quite liquid, while the veins from the muscles that had been thrown into tetanus were clotted solid. Upwards towards the heart the thrombus began to thin out just above the junction of the iliac veins, and it ceased half way between that point and the lower margin of the liver. From the junction of the iliac veins the clot was continued downwards for about an inch or less into the left iliac vein, thinning out as it was followed downwards. Below that point there was not a trace of clot in the iliac or femoral vein of the left side or in any of their tributaries.

2. A dog was chloroformed and both his eyes were atropinized. For that purpose an equal amount of 1 p.c. solution was used upon each eye. The left eye was blindfolded, and the light of a polarimeter oil lamp fitted with a plano-convex lens, was directed into the right eye from a distance of about a foot, the eye being fixed by means of a pair of fixation forceps. After an interval of some ten minutes, the usual amount of coagulating fluid was allowed to run into the femoral vein.

The post-mortem revealed the fact that all the vessels of the right eye stood out as dark prominent lines¹, while the vessels of the left retina were only just perceptible to the naked eye. On examining the ophthalmic veins at the back of either eyeball, that on the right side was with certainty ascertained to be clotted, it being possible to push little cylinders of clot out of the vessel when it was cut across. On the left side the blood in the ophthalmic

¹ I succeeded in getting a photograph of the retina of this eye the vessels appearing very clearly in it. The light however failed before I could secure a photograph of the left retina for comparison.

vein was as clearly made out to be liquid, the blood flowing away from the point of pressure when the back of a scalpel was pressed against the vein.

3. The chorda tympani was exposed on one side, and the sympathetic was separated from the vagus at the root, at the neck on the other side. Both nerves were then cut across and their peripheral ends were stimulated. The coagulating fluid was injected into the femoral vein, but no trace of coagulation was observed on either side in the veins emerging from the submaxillary gland.

On reviewing these facts it is evident that it is difficult to assume the formation of some new chemical body which favours coagulation under three such different conditions as those of asphyxia, muscle-tetanus and retinal stimulation. A more likely hypothesis would seem to be that an alteration in the gaseous composition of the blood is sufficient to determine its coagulation in the presence of tissue fibrinogens. It was evident that such a change would have to be sought for in either one of two directions, either in an increase of CO_2 or in a diminution of the O_2 in the blood.

The following protocol is conclusive as to an excess of CO_2 , sufficing of itself to determine the coagulability of the blood all over the body.

Oct. 1, 1890. Small fox-terrier put under chloroform tracheotomized. Trachea-tube placed in connection with a glass jar of some 3000 c.c. capacity standing over water containing a mixture consisting of 80 p.c. CO_2 and 20 p.c. O_2 . As the oxygen was absorbed more was added to make up the deficiency, the water thus being kept at the same level in the jar. Breathing slightly quickened but quiet. After an interval of some three minutes the coagulating fluid was run into the left femoral vein, the animal dying almost immediately.

P.M. Abdomen. Both iliac veins and I.V.C. clotted solid right up to heart. Hepatic vein and all its tributaries clotted. Portal vein contains only a slight clot but mesenteric veins are well clotted. Splenic vein not clotted. Renal veins firmly clotted.

Thorax. S.V.C., innominate veins and azygos, right heart and pulmonary artery one solid clot. Clot in the left heart, pulmonary veins and aorta.

Rest of body. No clotting in fore or hind limbs, all veins of head and neck clotted, including all the veins and sinuses of the brain.

Quite in harmony with this experiment is Wooldridge's observation that coagula occur in extra-portal tracts as well as in the portal area

when the injection of tissue fibrinogen is made in animals during active digestion, especially if their food has contained a large quantity of fat. The increased production of CO_2 during digestion, and especially after fatty food, is of course a common-place of physiology.

Further, the influence of CO_2 gas upon blood coagulation after injections of tissue fibrinogens is borne out in the following case. The injection of coagulating fluid had been made and the post-mortem as usual disposed the coagulation in the portal tract only. The blood from the systemic veins was collected and was still liquid after several hours and all the blood corpuscles had sunk to the bottom as in peptone plasma. The clear supernatant plasma which was decanted off, clotted immediately on passing CO_2 ¹ gas through it. A portion which was kept as a control was still liquid next morning.

Of some bearing also on the causation of the coagulation is the fact that the only instance I have seen where coagulation failed to occur after the injection of a tissue fibrinogen solution was that of a dog, which had been used for a class demonstration of the accelerator nerves, and which had become dead cold under the influence of the anaesthetic and of prolonged artificial respiration. In this case not a trace of coagulation was revealed by the post-mortem although the full quantity of coagulating fluid had been injected into the jugular. The coagulating fluid was immediately afterwards tested upon another dog and found to be perfectly active. In this case the lowering of the metabolism by cold and by the anaesthetic, the complete emptiness of the stomach as disclosed by the post-mortem and the efficient ventilation which was kept up, probably all contributed to the result by keeping down the amount of CO_2 to a minimum.

In view of these facts I think one may conclude with at least a certain amount of probability that the determination of the coagulation to the portal tract after an injection of tissue fibrinogens is due to an

¹ Wooldridge states that the blood from the extra-portal tracts, after any injection of coagulating fluid, remains not only liquid but also uncoagulable by CO_2 . Such is undoubtedly the rule, the observation reported above being an exception to it.

P.S. (April 1). I have since writing the above seen cause to believe that what I have characterized as the exception is really the rule. The blood collected from the extra-portal tracts after thrombosis of the portal vein very seldom fails to coagulate, if it is heated to 37°C . in a water-bath, and a stream of CO_2 is then passed through it; the comparative frequency of clotting in the veins of the body cavities (interior of skull, thorax, abdomen) as contrasted with the veins returning in the limbs is possibly determined by this factor of temperature.

excess of CO_2 in the blood of that region and that the amount of CO_2 in the systemic veins through which the injection is made, is in ordinary circumstances insufficient to bring about the coagulation of the blood there.

Having thus far studied the effects of an increase of CO_2 in the blood upon its coagulability, it remained still to be determined whether a deprivation of oxygen unaccompanied by a rise of CO_2 tension would favour coagulation in a similar manner. An animal was therefore tracheotomized and the trachea-tube was fitted with T-piece, inspiration being made through one limb which was brought into connection with a large vessel full of pure H_2 gas which was standing over water, while expiration took place freely into the outer air through the other limb, which was armed with a Speck's intestinal valve. Injection of the coagulating fluid was made through the femoral vein as soon as the respiration had become distressed. The usual prolonged respiratory standstill then took place and was followed by the few deep 'ante-mortem' gasps.

P.M. (Begun during the long pause.)

Thorax. A slight clot in the S.V.C. filling about one-fourth of its calibre. Azygos and intercostal veins clotted. I.V.C. not clotted. Right auricle clotted, slight clot in right ventricle. In left heart a few traces of clot. Aorta clotted right down to the origin of the iliacs. All these clots very dark in colour.

Abdomen. Only one or two mere shreds of clot in I.V.C. portal vein not clotted, rest of body blood in limbs everywhere liquid.

On this case it may be remarked that it can hardly be expected that the long respiratory standstill which is an invariable occurrence in asphyxia through acute deprivation of oxygen should run its course without a considerable rise in the CO_2 tension in the blood. It seems probable that the blood, which was in this case found coagulated in the descending aorta, was blood that had passed through the lungs during the respiratory pause, whereas the blood which was found liquid in the I.V.C. is more likely to have passed through the lungs before that pause took place, and therefore to have had an opportunity of freeing itself from its excess of CO_2 . The same holds of the blood of the S.V.C., which was liquid with the exception of that portion of it which came from the azygos vein.

The absence of a coagulum in the portal vein is with all probability due to the blocking of the aorta by clot. The liquidity of the blood in

the I.V.C. could of course not be explained in the same way, the injection having been made through the femoral vein.

Two methods of turning the difficulty introduced into the matter by the long respiratory pause suggested themselves.

(1) To ventilate with H_2 .

With the appliances at command I was only able to carry out this imperfectly. The coagulation was not limited to the portal district, but I was not able to satisfy myself that the ventilation had been adequate.

(2) To make the animal breathe out of a reservoir of CO gas. This was done, but when connection was made the respiration gradually became feebler and feebler. Ventilation was thus plainly inadequate, and the clots found on post-mortem examination were not limited to the portal area. The blood in the azygos and the intercostal veins however remained perfectly liquid. In this respect this case is the exact converse of the case quoted above, where after the violent respiratory struggles the azygos and its tributary intercostals were clotted solid. In fact it is easy to predict in an ordinary case from the character of the respirations whether the azygos will be found clotted or not.

After having pursued up to this point methods of direct enquiry into the conditions governing the distribution of the coagulation following upon the injection of Wooldridge's tissue fibrinogen I proceeded to investigate the changes introduced into the phenomena by the action of certain poisons. These experiments I hope to report upon more completely in a future communication.

It will suffice for the present to put upon record that when a dose of atropin is administered, such as is sufficient to dilate the pupil ad maximam and to paralyse the cardiac nerve-endings of the vagus, and presumably also the nerve-endings in the intestinal canal, an injection of Wooldridge's coagulating fluid was followed, in one case, by the usual coagulation of the portal area alone, the blood clot in the portal vein being however of the brightest arterial red. In two other cases the whole blood in the body was clotted solid, and here also everywhere, both in the arteries and also in the portal and systemic veins, the clots were of a brilliant arterial colour. I have also once seen the same bright arterial coloured clot in the portal vein after the administration of curare.

All the animals employed in these experiments were dogs. The coagulating fluid used was in all cases made from boars' testicles. The experiments were performed in the Physiological Laboratory of the University of Sydney.

P.S. Since writing the above I have studied the effects of Wooldridge's coagulating fluid on cats. I find that when respiration is going on normally, a moderate injection of Wooldridge's fluid is not followed by any coagulation either in the portal or in the systemic veins. When however asphyxia is produced in the animal and an injection of the same quantity of coagulating fluid is made at its height the blood coagulates throughout the whole vascular system.